

## CONTROL OF BLOOD-GAS AND ACID-BASE STATUS DURING ISOMETRIC EXERCISE IN HUMANS

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(Received 5 May 1987)

### SUMMARY

1. At a given level of pulmonary gas exchange, ventilation ( $\dot{V}_E$ ) is appreciably higher during isometric exercise than during isotonic exercise. It is presently not clear whether the resultant hypocapnia represents a compensatory hyperventilation for an arterial metabolic acidaemia or whether it might reflect a primary respiratory alkalaemia.

2. To resolve this issue, five subjects performed isometric leg exercise designed to induce exhaustion in *ca.* 5 min and, on a separate occasion, *ca.* 8 min.  $\dot{V}_E$ ,  $\text{CO}_2$  output ( $\dot{V}_{\text{CO}_2}$ ),  $\text{O}_2$  uptake ( $\dot{V}_{\text{O}_2}$ ) and end-tidal gas tensions ( $P_{\text{ET,CO}_2}$ ,  $P_{\text{ET,O}_2}$ ) were measured breath-by-breath during exercise and recovery; arterialized venous blood (drawn from the dorsum of the heated hand) was sampled frequently and analysed for  $P_{\text{CO}_2}$ ,  $P_{\text{O}_2}$ , pH, bicarbonate and lactate. These response profiles were compared with those resulting from exhausting bouts of isotonic leg exercise (cycle ergometry) of similar duration.

3. The isotonic exercise induced a metabolic (lactic) acidaemia with partial respiratory compensation. In contrast, isometric exercise consistently resulted in a respiratory alkalaemia, with little or no increase of blood [lactate]. At the end of the isometric exercise,  $\dot{V}_E$  fell abruptly and then rose again after a short interval (20 s, on average). This secondary stimulation presumably reflected the acid-base consequences of the increased blood [lactate] (3–5 mM, on average) which occurred in the recovery phase.

4. We therefore conclude that a primary respiratory alkalaemia occurs during isometric exercise, and that this results from ventilatory stimulation at a time when the 'exercise' metabolites are trapped within the contracting muscles as a consequence of impeded blood flow. The initial rapid reduction of ventilation which occurred at the cessation of the isometric exercise is consistent with a washing-out of 'hyperpnoea-inducing' metabolites from the muscles. Allowing for transit to the central circulation, the reduced ventilation is subsequently supplemented by a powerful humoral drive to breathe which results in a further hyperpnoea and secondary hypocapnia. Because of its latency, we hypothesize that this secondary hypocapnia is of peripheral chemoreceptor origin.

5. The ventilatory response profile for isometric exercise, and the subsequent

recovery phase, supports the contention that both the exercising muscles and the peripheral chemoreceptors can be important sites for inducing hyperpnoea in humans.

## INTRODUCTION

Fatiguing isometric contractions of large (Whipp & Phillips, 1970) or small (Wiley & Lind, 1971, 1975; Duncan, Johnson & Lambie, 1981) muscle groups have been shown to induce hyperventilation often resulting in marked alveolar (end-tidal) hypocapnia. However, it is not clear whether this hyperventilation represents a respiratory compensation for an exercise-induced lactic acidemia or, alternatively, whether it is a primary respiratory alkalemia resulting from reflexogenic ventilatory stimulation (e.g. involving pressure, metabolite and pain receptors) from the contracted muscles and/or 'central command' influences on the ventilatory control mechanisms.

Based upon studies of muscle metabolism during short-term fatiguing isometric exercise bouts (Ahlborg, Bergstrom, Ekelund, Guarnieri, Harris, Hultman & Nordesjo, 1972; Edwards, Hill & McDonnell, 1972; Funderburk, Karlsson & Lind, 1972; Karlsson & Olander, 1972; Karlsson, Funderburk, Essén & Lind, 1975; Tesch & Karlsson, 1979), we hypothesized that fatiguing isometric contractions (of approximately 5–8 min duration) would effectively occlude the vascular beds of the contracted muscles, thereby forcing an obligatory anaerobiosis with a consequent rise in [lactate],  $[H^+]$  and the concentrations of other metabolites within the contracted muscle. However, this condition would not be reflected in the blood until the recovery phase, when these metabolites would subsequently be 'flushed' into the central circulation with restoration of local perfusion.

To test this hypothesis, we determined the temporal profiles of the ventilatory, pulmonary gas exchange, blood-gas and acid-base responses which resulted from isometric contractions of the legs performed to the point of fatigue and from the subsequent recovery phase. These responses were then compared with those obtained from equivalent fatiguing bouts of isotonic leg exercise.

## METHODS

Five healthy subjects (three males, two females) gave their informed consent to participate in this investigation. Their age, height and weight (mean  $\pm$  s.e.m.) were  $28 \pm 3$  years,  $172.1 \pm 4.5$  cm and  $67.9 \pm 6.5$  kg, respectively. Each subject performed four fatiguing exercise tests with the legs: two isometric (*ca.* 5 and 8 min) and two isotonic (*ca.* 5 and 8 min) (Table 1). These tests were performed in a randomized order on separate days with the subjects at least 12 h post-absorptive. Isometric exercise was performed on a 'leg-press' machine with the subject in the seated position: the load was supported primarily by the quadriceps femoris muscles at a knee angle of 90–110 deg which remained constant throughout each test and was the same for each particular subject on both tests. The isotonic exercise consisted of cycling on a friction-braked cycle ergometer (Monark, Model 668) at a speed of 60 r.p.m. In each instance, the exercise was stopped when the subject could no longer support the load (isometric test) or sustain the required power output (isotonic test); this was taken to represent the point of fatigue. During each test, expired airflow was measured with a pneumotachograph (Rudolph, 3800) downstream of the expiratory port of the low-resistance breathing valve (Rudolph, 2700, dead space: 90 ml), connected to a variable-reluctance manometer (Validyne, MP45:  $\pm 2$  cmH<sub>2</sub>O); the pneumotachograph was maintained at 37 °C by a thermal feed-

back device, and calibrated by inputting known volumes of room air at several mean flows. Rapidly responding analysers continuously monitored  $P_{\text{CO}_2}$  (Datex CD 101; 90% response time: 0.1 s) and  $P_{\text{O}_2}$  (Applied Electrochemistry, S3A; 90% response time: <0.08 s) in respired gas sampled from the mouthpiece; precision-analysed gas mixtures were used for their calibration. Heart rate was derived beat-by-beat from the R-R interval of an ECG signal (Birtcher, 7000). The electrical signals from these devices underwent analog-to-digital conversion and computer analysis (Tektronix, 4052) for on-line, breath-by-breath determination of ventilation ( $\dot{V}_E$ , BTPS),  $\text{CO}_2$  output ( $\dot{V}_{\text{CO}_2}$ , STPD),  $\text{O}_2$  uptake ( $\dot{V}_{\text{O}_2}$ , STPD), ventilatory equivalents for  $\text{CO}_2$  and  $\text{O}_2$  ( $\dot{V}_E/\dot{V}_{\text{CO}_2}$ ,  $\dot{V}_E/\dot{V}_{\text{O}_2}$ ), respiratory exchange ratio ( $R$ ) and end-tidal  $P_{\text{CO}_2}$  and  $P_{\text{O}_2}$  ( $P_{\text{ET,CO}_2}$ ,  $P_{\text{ET,O}_2}$ ).

Arterialized venous blood was drawn from an indwelling 18 gauge catheter inserted into a superficial vein on the dorsum of a heated hand (Forster, Dempsey, Thompson, Vidruk & Dopico, 1972). Samples were drawn during the steady states of rest for the isometric tests and unloaded pedalling for the isotonic tests, and at regular intervals throughout the work and subsequent

TABLE 1. Characteristics of isometric and isotonic exercise

Subject	Work load				Time to fatigue (s)			
	Isometric (kg)		Isotonic (W)		Isometric		Isotonic	
	Low	High	Low	High	Low	High	Low	High
1	63.6	81.8	275	300	517	226	656	285
2	90.9	109.1	320	380	479	387	546	303
3	81.8	100.0	280	330	456	335	532	326
4	54.5	72.7	190	210	497	292	408	273
5	54.5	72.7	190	260	445	314	473	382
Mean	69.1	87.3	251	296	480	311	523	314
$\pm$ S.E.M.	8.3	8.3	29	33	15	30	46	22

recovery phases: 2 ml samples were drawn for analysis of lactate by a standard enzymatic technique (Hohorst, 1963), and separate 2 ml samples for the measurement of  $P_{\text{O}_2}$ ,  $P_{\text{CO}_2}$  and pH and the calculation of  $[\text{HCO}_3^-]$  in duplicate using standard electrodes (Instrumentation Laboratories, 1303) calibrated before and after each measurement with certified standard buffers and gas mixtures.

Differences between responses were assessed by a paired-comparisons  $t$  test ( $P < 0.05$ ).

## RESULTS

One of the most striking features of the isometric exercise tests was the absence of a marked increase of blood [lactate] during the exercise: in the high-load test, there was no increase in [lactate] whatsoever; in the low-load test, however, there was evidence of a rise in [lactate] levels in the exercise, although this was modest at most (i.e. 2–3 mM; Fig. 1). This response pattern contrasted strikingly with that for the isotonic exercise; this produced a rapid and substantial increase of blood [lactate] to an average of about 8 mM by the end of the exercise (Fig. 1). During early recovery from the isometric exercise, there was a sharp increase of blood [lactate] which peaked some 2–4 min into recovery at an average value of 4–5 mM; the lactate levels were still elevated above resting at the end of the 10 min recovery phase. The peak blood lactate levels in recovery during the isotonic tests were higher than for the isometric tests (i.e. 8–10 mM, on average), but also occurred within 2–4 min of recovery; again [lactate] was still elevated at the end of the recovery phase.

Consequently, because the response profile of  $P_{\text{CO}_2}$  during both types of exercise

was similar, this resulted in a dichotomous pH response between the two forms of exercise (Figs 1 and 2). The hypocapnia represented a primary respiratory alkalaemia for the isometric exercise (i.e. for the low-load tests, pH at fatigue averaged 7.48 and  $P_{\text{CO}_2}$  27.4 Torr; for the high-load tests, the corresponding values were 7.47 and 27.1 Torr, respectively), but a partial respiratory compensation for a primary metabolic acidaemia during the isotonic exercise (i.e. for the low-load tests pH averaged 7.28 at fatigue and  $P_{\text{CO}_2}$  29.1 Torr; for the high-load tests, the corresponding values were 7.28 and  $P_{\text{CO}_2}$  33.4 Torr, respectively: Figs 1 and 2).

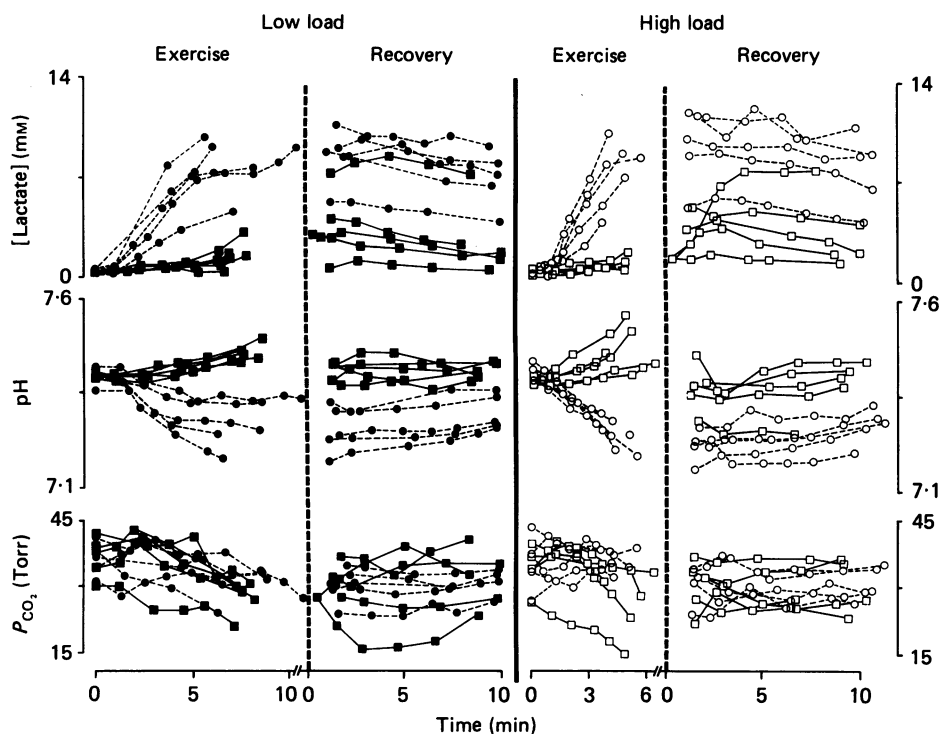


Fig. 1. Individual response profiles of blood lactate ([lactate]), pH and  $P_{\text{CO}_2}$  in arterialized venous blood during isometric exercise (■, □; continuous lines) and isotonic exercise (●, ○; dashed lines) and subsequent recovery. Left panel: low load (filled symbols). Right panel: high load (open symbols).

During recovery from the isometric exercise, a marked acidaemic shift was evident in the blood (Figs 1 and 2), with pH falling to an average of 7.42 on the low-load tests in early recovery and 7.34 on the high-load tests; this most likely reflected an influx of hydrogen ions into the circulation (presumably from lactic acid). The recovery from the isotonic exercise was also characterized by an acidaemic shift. The magnitude of this pH fall was less striking than for the recovery from the isometric exercise. However, as the pH during the work was lower for the isotonic tests, it attained lower absolute values in the recovery phase than was the case for the isometric tests (Figs 1 and 2). At the end of the recovery phase, for both the isometric and isotonic tests, blood pH and  $P_{\text{CO}_2}$  were only partially restored towards resting levels.

The time course of the  $\dot{V}_E$ ,  $\dot{V}_{CO_2}$  and  $\dot{V}_{O_2}$  responses to the isometric and isotonic exercise are displayed in Fig. 3 for a representative subject. Mean end-exercise responses are presented in Table 2. At the onset of the isometric exercise,  $\dot{V}_E$  manifested a slow but systematic rise which was followed, some minutes later, by a more rapid increase until fatigue ensued (Fig. 3). In contrast, at the onset of the isotonic exercise,  $\dot{V}_E$  increased rapidly and then continued to rise somewhat more

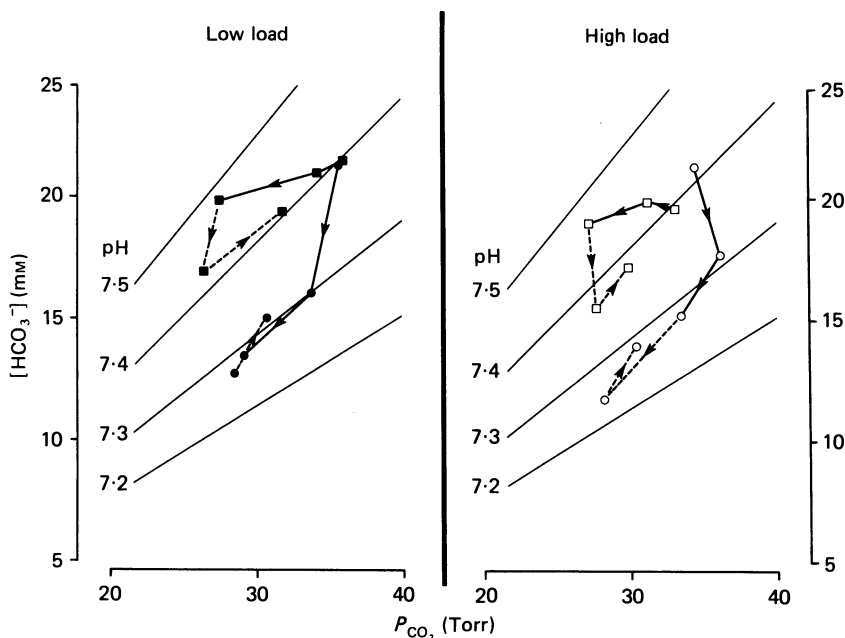


Fig. 2. Mean temporal relationships between blood bicarbonate concentration ( $[HCO_3^-]$ ) and  $P_{CO_2}$  for isometric tests (■, □; continuous lines) and isotonic tests (●, ○; dashed lines) at the start, mid-point and end of exercise and at the start, mid-point and end of the subsequent recovery. Radiating lines represent pH isopleths. Standard error bars have been omitted for clarity. Left panel: low load (filled symbols). Right panel: high load (open symbols).

slowly throughout the remainder of the exercise (Fig. 3).  $\dot{V}_{O_2}$  increased in a virtually linear fashion during the course of the isometric exercise; this response differed markedly from that of the isotonic exercise (Fig. 3) which demonstrated the earlier rapid and the later slower phases of the kinetics which is characteristic of high-intensity isotonic exercise (reviewed by Whipp & Mahler, 1980).

Although the absolute level of  $\dot{V}_E$  at end-exercise was appreciably higher for the isotonic exercise than for the isometric exercise, when related to the rates of pulmonary gas exchange,  $\dot{V}_E$  was in fact greater for the isometric (Table 2). Thus, the ventilatory equivalents for  $O_2$  and  $CO_2$  ( $\dot{V}_E/\dot{V}_{O_2}$ ,  $\dot{V}_E/\dot{V}_{CO_2}$ ) attained far higher values during the isometric exercise (at fatigue,  $\dot{V}_E/\dot{V}_{O_2} = 53$  and  $\dot{V}_E/\dot{V}_{CO_2} = 45$  on average, for the low-load tests; the corresponding values for the high-load tests were 68 and 43, respectively) than during the isotonic exercise (for the low-load tests  $\dot{V}_E/\dot{V}_{O_2} = 40$

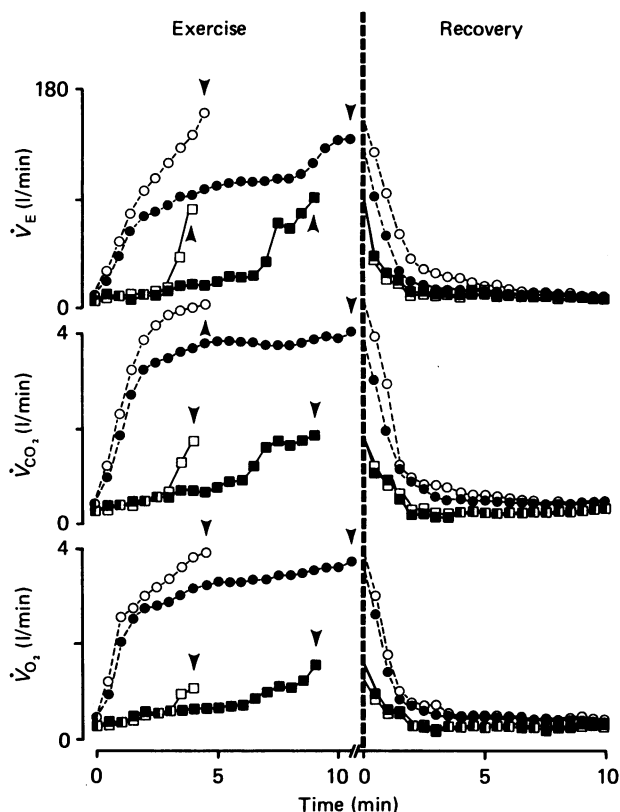


Fig. 3. Response profiles of ventilation ( $\dot{V}_E$ ),  $\text{CO}_2$  output ( $\dot{V}_{\text{CO}_2}$ ), and  $\text{O}_2$  uptake ( $\dot{V}_{\text{O}_2}$ ) to isometric exercise ( $\blacksquare$ ,  $\square$ ; continuous lines) and isotonic exercise ( $\bullet$ ,  $\circ$ ; dashed lines) and subsequent recovery for a representative subject (subject 1). Arrows denote point of fatigue for each test. Low load (filled symbols). High load (open symbols).

and  $\dot{V}_E/\dot{V}_{\text{CO}_2} = 35$  at fatigue; the corresponding values for the high-load tests were 40 and 33, respectively).

#### DISCUSSION

Numerous studies in humans have demonstrated that muscle blood flow becomes severely restricted or even non-existent above approximately 30% of the maximum voluntary contraction of the leg muscles (Barcroft & Millen, 1939; Edwards *et al.* 1972; reviewed by Shepherd, Blomqvist, Lind, Mitchell & Saltin, 1981; Sejersted, Hargens, Kardel, Blom, Jensen & Hermansen, 1984). Therefore, while isometric contractions at 15% maximum voluntary contraction have been shown to have little effect on intramuscular [lactate] and [pyruvate] (Ahlborg *et al.* 1972) and can be sustained for prolonged periods (Monod & Scherrer, 1965), muscle lactate and pyruvate levels are both increased substantially during isometric contractions in excess of  $\sim 30\%$  maximum voluntary contraction and the intramuscular concentration of creatine phosphate is reduced (Karlsson & Olander, 1972; Funderburk

*et al.* 1972; Edwards *et al.* 1972; Karlsson *et al.* 1975; Tesch & Karlsson, 1979); as a result, the tolerable duration of the contraction was reduced (Monod & Scherrer, 1965). While we were not able to measure intramuscular metabolites during the present investigation, our results are consistent with these findings.

Furthermore, our investigation demonstrates that the alveolar hypocapnia found during fatiguing isometric contractions (Whipp & Phillips, 1970; Wiley & Lind, 1971, 1975; Duncan *et al.* 1981; Poole, Ward & Whipp, 1986) results in a primary

TABLE 2. End-exercise values for O<sub>2</sub> uptake, CO<sub>2</sub> output, ventilation and heart rate (HR)

Subject	Low				High			
	$\dot{V}_{O_2}$ (l/min)	$\dot{V}_{CO_2}$ (l/min)	$\dot{V}_E$ (l/min)	HR (bt/min)	$\dot{V}_{O_2}$ (l/min)	$\dot{V}_{CO_2}$ (l/min)	$\dot{V}_E$ (l/min)	HR (bt/min)
Isometric								
1	1.60	1.85	91	148	1.07	1.71	81	155
2	1.81	2.02	63	153	1.68	2.74	84	155
3	0.97	1.32	52	160	0.96	1.86	60	154
4	1.14	1.59	98	178	1.32	1.97	109	176
5	0.76	0.72	29	118	0.85	1.12	65	137
Mean	1.26	1.50	67	151	1.18	1.88	80	155
± S.E.M.	0.22	0.25	14	11	0.17	0.29	10	7
Isotonic								
1	3.67	4.02	138	179	3.83	4.62	162	180
2	4.29	4.91	151	177	4.48	5.41	155	166
3	3.40	4.07	141	175	3.64	4.70	151	172
4	2.10	2.25	101	177	2.07	2.31	97	179
5	2.39	2.58	100	175	2.70	3.29	110	163
Mean	3.17	3.57	126	177	3.34	4.07	135	172
± S.E.M.	0.45	0.56	12	1	0.48	0.60	15	4

respiratory alkalaemia (Figs 1 and 2) as a consequence of the ventilatory response (Table 2 and Fig. 3) occurring at a time when the exercise-generated metabolites are presumably trapped within the contracting muscles. This contrasts with our results obtained with high-intensity fatiguing isotonic exercise, where the large increases in blood lactate levels and decreases in blood pH continued to the point of fatigue (Figs 1 and 2). And, while there is considerable debate regarding the precise spectrum of neural (centrogenic and reflexogenic) and humoral mechanisms which underlie the hyperpnoea of isotonic exercise in humans, one important component of the hyperpnoeic response during high-intensity isotonic exercise appears to result from acidaemic stimulation of the carotid body (reviewed by Whipp, 1983). Furthermore, it has been argued that, based upon exercise studies in subjects with complete spinal-cord lesions, reflexogenic stimulation arising from the exercising muscles does not occupy an obligatory role in the control of ventilation during isotonic exercise (Adams, Frankel, Garlick, Guz, Murphy & Semple, 1984). Although, in the present investigation, the end-tidal  $P_{CO_2}$  was reduced to similar levels during the isometric and the isotonic exercise, it is most likely that the ventilatory stimulus in the two conditions arose from different sources.

There is considerable disagreement as to the source of the ventilatory drive during

isometric contractions of skeletal muscle. Studies in the rabbit and dog have suggested that the drive is reflexogenic, arising wholly from within the contracted muscle itself (e.g. Tallarida, Baldoni, Peruzzi, Raimondi, Massaro & Sangiorgi, 1981; Tallarida, Baldoni, Peruzzi, Raimondi, DiNardo, Massaro, Visigalli, Franconi & Sangiorgi, 1985). In contrast, studies in man have implicated supraspinal mediation (Muza, Lee, Wiley, McDonald & Zechman, 1983) which may operate in combination with reflexogenic drives (Wiley & Lind, 1971, 1975; Duncan *et al.* 1981).

The selective neural blockade experiments of McCloskey & Mitchell (1972) have demonstrated that, at least in the cat, stimulation of the smaller myelinated and non-myelinated afferent fibres (groups III and IV) during sustained maximal isometric contractions of the hindlimbs can evoke ventilatory and cardiovascular stimulation; this observation has recently been corroborated for phasic isometric contractions (Mense & Stahnke, 1983). Studies in the cat which have examined the differential effects of experimentally induced ischaemia in isometrically exercising muscle on afferent discharge patterns have suggested that group IV afferents (Mense & Stahnke, 1983; Kaufman, Rybicki, Waldrop & Ordway, 1984) and type 'N' nociceptive afferents (Mense & Stahnke, 1983) are preferentially activated under these conditions. In contrast, the larger, myelinated fibres (groups I and II) do not appear to subserve any appreciable role in ventilatory or cardiovascular control during isometric exercise (Waldrop, Rybicki & Kaufman, 1984).

In humans, also, Duncan *et al.* (1981) have argued that afferents from the contracting muscles provide an important source of ventilatory drive during isometric exercise. These authors demonstrated that, in contrast to normal subjects, patients with sensory loss from the forearm (consistent with the absence of intact muscle afferent projections) developed a markedly reduced hyperpnoea during sustained isometric hand-grip exercise, with no evidence of hyperventilation (cf. Figs 1 and 2). In apparent contrast, Wiley & Lind (1971) reported that circulatory occlusion following isometric hand-grip exercise in normal subjects did not prevent  $\dot{V}_E$  from returning to resting levels, an observation which was thought to be inconsistent with an important reflexogenic ventilatory drive during and following isometric exercise. It should be pointed out, however, that in the latter investigation only two subjects (the authors) were studied, and furthermore that the exercise end-point was selected on the basis of previous tests rather than being prolonged to fatigue.

Voluntary and electrically induced isometric exercise in humans which is designed to be confined solely to the quadriceps femoris muscles has been shown to produce equivalent increases in both heart rate and blood pressure (Hultman & Sjöholm, 1982), a finding which led these authors to conclude that intramuscular receptors had the capacity to evoke the *entire* pressor response under these conditions. However, Leonard and colleagues (Leonard, Mitchell, Mizuno, Rube, Saltin & Secher, 1985) observed that the magnitude of heart rate and blood pressure responses to voluntary isometric exercise of the quadriceps femoris muscles both increased proportionally with the 'sense of effort' when an equivalent force was exerted under conditions of partial neuromuscular blockade, leading to the conclusion that both central command and reflex neural mechanisms are of importance. However, these two control mechanisms appear to exhibit redundancy rather than being additive and

therefore, in any particular situation, the larger response is likely to predominate. Regrettably, the ventilatory response to the exercise was not measured in either of these studies. Furthermore, it has not, as yet, been determined whether there are different subpopulations of group III and IV projections from muscle which subserve ventilatory and cardiovascular control during isometric exercise, or whether there is a parallel drive from a common source to the central respiratory and cardiovascular integrating centres.

Despite the likelihood that the contracted muscle received little or no blood flow during the isometric exercise in our experiments,  $\dot{V}_{O_2}$  continued to rise throughout the exercise (Fig. 3). A similar response was observed by Kilbom & Persson (1982) during isometric contraction of the quadriceps femoris muscles at  $\sim 25$ – $30\%$  maximum voluntary contraction (i.e. above the level at which intramuscular pressure exceeds systolic blood pressure: Edwards *et al.* 1972). The increase in  $\dot{V}_{O_2}$  in the latter study (from 31 to 165 ml/min) was accompanied by an increase in leg blood flow (from 0.35 to 1.22 l/min); that is, a response which was entirely consistent with the relationship between these two variables which obtains for isotonic exercise. These authors concluded that an involuntary activation of leg muscles other than the quadriceps femoris likely accounted for this effect. We suggest that this occurred also in our isometric exercise tests and was responsible, in part, for the increased  $\dot{V}_{O_2}$  during the exercise (Fig. 3). Other potential sources for this augmented  $\dot{V}_{O_2}$  include an increased  $O_2$  cost of ventilatory and cardiac muscular work, metabolic stimulation arising from greatly increased catecholamine levels (Kozłowski, Brzezinska, Nazar, Kowalski & Franczyk, 1973), and also the stimulatory effect of hypocapnic alkalaemia on  $\dot{V}_{O_2}$  (Cain, 1970; Karetzky & Cain, 1970).

In our isometric exercise experiments,  $\dot{V}_{CO_2}$  increased proportionally more than  $\dot{V}_{O_2}$ , causing the respiratory exchange ratio ( $R$ ) to exceed unity for a considerable portion of the tests. This reflects a reduction in the  $CO_2$  stores of arterial blood (and other non-contracting tissues) consequent to the hyperventilation. It is doubtful that bicarbonate buffering of lactic acid contributed significantly as blood lactate levels did not rise until the later stages of the low-load isometric tests and even then only moderately (i.e.  $<2$ – $3$  mM: Fig. 1), while in the high-load isometric tests blood [lactate] showed little or no change throughout the entire duration of the exercise (Fig. 1). It is probable that the modest increase in blood [lactate] observed during the low-load tests reflects a small degree of lactate seepage from regions of the contracted muscle where the blood flow was not wholly impeded, it having been suggested that, at any given isometric force production, there exists a range of intramuscular pressure (Saltin, Sjogaard, Gaffney & Rowell, 1981; Sejersted *et al.* 1984).

The mean arterial blood pressure is increased by both fatiguing (Whipp & Phillips, 1970) and non-fatiguing isometric exercise, and to a greater extent than during comparable bouts of isotonic exercise (reviewed by Asmussen, 1981). It has been shown in anaesthetized dogs, under hypoxic conditions, that the peripheral chemoreceptors are inhibited by arterial hypertension (Heistad, Abboud, Mark & Schmid, 1974; Attinger, Attinger, Cooperson & Gottschalk, 1976) and it has been suggested that this effect is mediated via a central neural interaction of chemoreceptor and baroreceptor inputs (Heistad *et al.* 1974). It is pertinent to our investigation that this effect was found to be barely detectable under normoxic

conditions; that is, although it is possible that increases in arterial blood pressure may have influenced ventilation in our study, the magnitude of any ventilatory constraint which may be attributable to this mechanism under the conditions of our experiments is likely to be so small as to be of questionable significance.

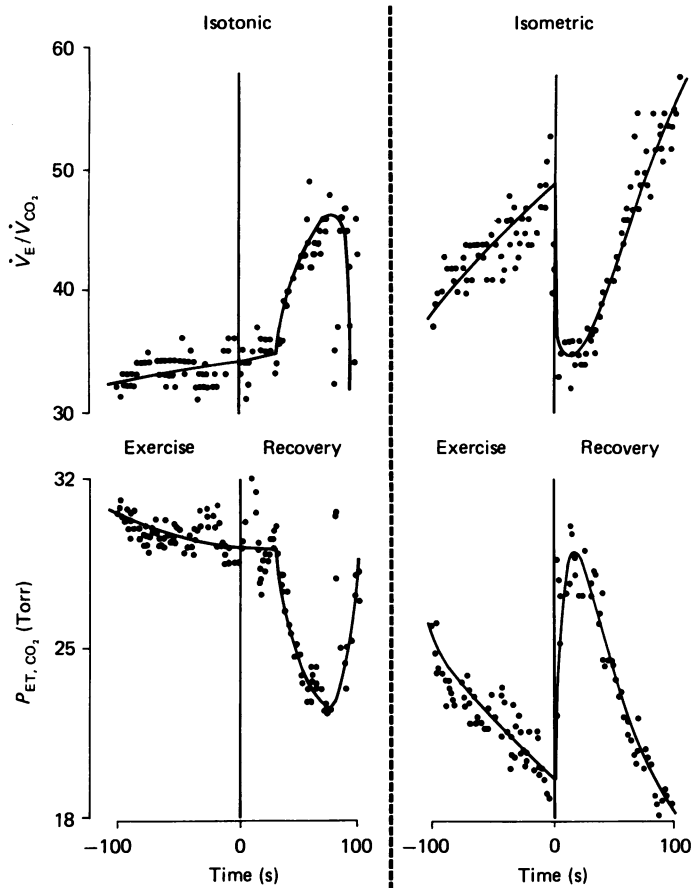


Fig. 4. Breath-by-breath responses of end-tidal  $P_{\text{CO}_2}$  ( $P_{\text{ET,CO}_2}$ ) and ventilatory equivalent for  $\text{CO}_2$  ( $V_E/V_{\text{CO}_2}$ ) across the exercise-recovery transition for a representative subject (subject 4). Left panel: isotonic exercise. Right panel: isometric exercise.

The arterial hypocapnia of isometric exercise might be expected to constrain the magnitude of the primary hyperventilatory response to the work by directly restraining the peripheral chemoreceptors. In addition, the hypocapnia presumably causes a reduction in cerebrospinal fluid  $P_{\text{CO}_2}$ , a condition which may restrain the activity of the central chemoreceptors. A further source of ventilatory constraint may also arise from an efferent inhibitory pathway which, in the cat, has been shown to project from the brain stem to the carotid body by way of the carotid sinus nerve (Neil & O'Regan, 1971), and which can be activated by an increase in cerebrospinal fluid pH (Majcherczyk & Willshaw, 1977). Regardless of the magnitude of such influences, however, the hyperpnoeic drive induced during the isometric exercise in

our investigation was clearly powerful enough to sustain high levels of ventilation (Table 2 and Fig. 3).

Because of the large blood-gas and acid-base changes which occurred during the exercise-recovery transition (Figs 1 and 2), we inspected this region of the tests more closely in order to gain further insight into possible mechanisms underlying the ventilatory responses to the isometric exercise (Fig. 4). It became evident (Figs 2 and 4) that, although the response profile of  $\dot{V}_E/\dot{V}_{CO_2}$  and  $P_{ET,CO_2}$  was generally consistent with the blood-gas and acid-base responses, its temporal response characteristics at the transition were too rapid to be discerned accurately from blood measurements. At the end of both the isotonic and isometric exercise, a marked hyperventilation was evident (i.e.  $\dot{V}_E/\dot{V}_{CO_2}$  was high and  $P_{ET,CO_2}$  was low), with the hyperventilation being more pronounced during the isometric exercise (Fig. 4). During the initial phase of the recovery from the isotonic exercise, the hyperventilatory response continued to develop at an essentially similar rate to that seen during the later stages of the exercise. However, some 20–30 s into the recovery, a marked secondary hyperventilation became evident ( $\dot{V}_E/\dot{V}_{CO_2}$  rising sharply) driving the  $P_{ET,CO_2}$  down by some 7–8 Torr: this occurred at a time when the blood [lactate] was overshooting and the pH undershooting (Fig. 1).

In contrast to the isotonic exercise response, the recovery from the isometric exercise produced a rapid and immediate hypoventilation in synchrony with cessation of the exercise; i.e.  $\dot{V}_E/\dot{V}_{CO_2}$  fell abruptly and  $P_{ET,CO_2}$  rose by some 12 Torr with no discernible delay (Fig. 4). After approximately 20–30 s, this was replaced by a marked subsequent hyperventilation of sufficient intensity to drive  $P_{ET,CO_2}$  down below the end-exercise level.

We interpret this pattern of ventilatory and gas exchange response at the exercise-recovery transition for isometric exercise to be consistent with the removal of a powerful ventilatory drive (likely arising reflexogenically from metabolites trapped within the contracted muscles) as the post-exercise hyperaemia flushes these 'hyperpnoea-inducing' metabolites from the muscles. Following their transit to the central circulation, we propose that this is subsequently exchanged for a powerful humoral drive to breathe which results in a secondary hypocapnia. Because of its latency and the superimposition of a metabolic acidemic shift in acid-base status, we hypothesize that this secondary hypocapnia is of peripheral chemoreceptor origin.

The authors express their gratitude to the Medical Graphics Corporation, St Paul, MI, U.S.A., and Ludwig Gym Equipment Company, Newbury Park, CA, U.S.A., for the loan of equipment, Dr Imad Rasool for placement of the venous cannulae, and Dr Arthur Vailas for laboratory facilities. We thank Elyse Oishi for typing the manuscript.

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